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APPLICATION NUMBER: 60/345,634

FILING DATE: January 03, 2002

RELATED PCT APPLICATION NUMBER: PCT/US03/00072



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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Gary M. Steven J.	Hieftje Ray	Bloomington, IN Bloomington, IN


☐ Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

A MULTIPLE-SOURCE TOFMS FOR THE SIMULTANEOUS ACQUISITION OF CHEMICAL INFORMATION FROM TWO DISTINCT IONIZATION SOURCES

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages

17

☐ CD(s), Number

☒ Drawing(s) Number of Sheets

21

☒ Other (specify)

Invention Disclosure (3 pages)
Abstract (2 pages)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

- ☒ Applicant claims small entity status. See 37 CFR 1.27.
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\$80.00

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☐ Yes, the name of the U.S. Government agency and the Government contract number are _____

Respectfully submitted,

SIGNATURE

Date

1/3/02

TYPED or PRINTED NAME

Bradford G. Addison

REGISTRATION NO.

41,486

(if appropriate)

Docket Number:

29920-69648

TELEPHONE

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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11 Mendian Street
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group: Unknown

Confirmation No.: Unknown

Application No.: Unknown

Invention: A MULTIPLE-SOURCE TOFMS
FOR THE SIMULTANEOUS
ACQUISITION OF CHEMICAL
INFORMATION FROM TWO
DISTINCT IONIZATION
SOURCES

Applicant: Gary M. Hieftje, et al.

Filed: Herewith (1/3/02)

Attorney

Docket: 29920-69648

Examiner: Unknown

CERTIFICATE UNDER 37 C.F.R. § 1.10

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Respectfully submitted,

BARNES & THORNBURG

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INDS02 BADDISON 421712v1

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT

\$80.00

Complete If Known

Application Number	Unknown
Filing Date	Herewith (1/3/02)
First Named Inventor	Gary M. Hieftje, et al.
Examiner Name	Unknown
Group Art Unit	Unknown
Attorney Docket No.	29920-69648

METHOD OF PAYMENT

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- ☐ Charge Any Additional Fee Required
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- ☒ Applicant claims small entity status
See 37 CFR § 1.27

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code (\$)	Fee Code (\$)	Fee Code (\$)	Fee Code (\$)		
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	80.00
SUBTOTAL (1)					\$80.00

2. EXTRA CLAIM FEES

		Extra Claims		Fee from below		Fee Paid
Total Claims	<input type="text"/>	-20** =	<input type="text" value="0"/>	X	<input type="text"/>	= <input type="text" value="0.00"/>
Independent Claims	<input type="text"/>	-3** =	<input type="text" value="0"/>	X	<input type="text"/>	= <input type="text" value="0.00"/>
Multiple Dependent					<input type="text"/>	= <input type="text"/>
Large Entity		Small Entity		Fee Description		
Fee Code (\$)	Fee (\$)	Fee Code (\$)	Fee (\$)			
103	18	203	9	Claims in excess of 20		
102	84	202	42	Independent claims in excess of 3		
104	280	204	140	Multiple dependent claim, if not paid		
109	84	209	42	** Reissue independent claims over original patent		
110	18	210	9	** Reissue claims in excess of 20 and over original patent		
SUBTOTAL (2)				<input type="text" value="\$0.00"/>		

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code (\$)	Fee Code (\$)	Fee Code (\$)	Fee Code (\$)		
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non - English specification	
147	2,520	147	2,520	For filing a request for ex parte reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR § 1.17(q)	
126	180	126	180	Submission of Information Disclosure Statement	
681	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3)

SUBMITTED BY

Name (Print/Type)

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Registration No.
(Attorney/Agent)

41,486

Complete (if applicable)

Telephone

(317) 231-7253

Signature

Bradford G. Addison

Date

1/3/02

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PROVISIONAL PATENT APPLICATION

of

Gary M. Hieftje
(Bloomington, IN)

Steven J. Ray
(Bloomington, IN)

for

A MULTIPLE-SOURCE TOFMS FOR THE SIMULTANEOUS
ACQUISITION OF CHEMICAL INFORMATION
FROM TWO DISTINCT IONIZATION SOURCES

ARTI-0211

Attorney Docket 29920-69648

**A Multiple-Source TOFMS for the Simultaneous
Acquisition of Chemical Information from Two Distinct
Ionization Sources**

Steven J. Ray and Gary M. Hefliger

Indiana University, Department of Chemistry, Bloomington, IN 47405

Concept:

The purpose of this invention is the simultaneous acquisition of several distinct forms of chemical information with regard to a mixture in order to better identify specific metals, their concentrations, ~~and~~ their associations and chemical speciation. This goal is accomplished by using established separation methods succeeded by chemical analysis by means of a unique detection system. The detection system is composed of a novel time-of-flight mass spectrometer.

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1st H₂O - Source

General Description:

In its preferred embodiment, the invention consists of a mixture separation step followed by mass spectrometric analysis. This experimental concept is depicted schematically in Figure 1. The separation is employed to segregate distinct chemical species that contain the identical metal from one another. It is noteworthy that such a system does not require the comprehensive separation of all species in the mixture, since the ability to match a single metal, elemental, or isotopic profile with a corresponding molecular ion spectrum allows non-ideal separations to be overcome. The mixture separation might be accomplished by liquid chromatography, capillary electrophoresis, or any number of separation techniques known in the literature. After separation, the effluent is split with a predetermined volume ratio and ^{or more} each separate stream injected into one of two different ionization sources. In this example, one of the sources is selected for its ability to provide speciation information (e.g. electrospray ionization); the other selected for its ability to provide very sensitive elemental determinations (e.g. the

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inductively coupled plasma). Generally the sources are selected based on their ability to provide independent types of chemical information.

Both of these sources are sampled simultaneously by a single mass spectrometer, and the detection of the ions produced by each accomplished in a parallel, simultaneous, ^{or sequential} multiplexed fashion. In this way, the desired chemical information is obtained virtually simultaneously from a single separation.

1. The SIMION software package is offered by Ion Source Software, the web site for which is: <http://www.srv.net/~klack/simion.html>. SIMION can be purchased in the US through Scientific Instrument Services, Inc., whose web site is: <http://www.sisweb.com/simion.htm>. This latter web site includes a substantial amount of background information about SIMION.
2. The GBC instrument, an ICP-TOFMS system, is one that might readily be modified to accommodate a second simultaneous ion source. However, there are others on the market that would also serve. The GBC Scientific Equipment web site is: <http://www.gbcsi.com/>. The full name of the GBC instrument is the "Optimass 8000 ICP-TOFMS", described more fully at: http://www.gbcsi.com/products/icp_tof/optimass.asp

Separation:

While analysis of a single chemical compound is certainly possible, there is a great advantage in using the described system in association with a separation technique. In this manner it is possible to provide unambiguous identification of analytes within the mixture in question, to overcome intra-separation error, and to take advantage of the orthogonal (independent) nature of the chemical information provided by the two different ionization sources. Many separation techniques are routinely employed, are described within the literature, and will be selected depending upon the applications in which they have been shown to be effective. The preferred embodiment of this invention uses two different ionization sources: electrospray ionization (ESI) and the inductively coupled plasma (ICP). As several authors have noted (1-5), these sources are complementary in both the type of information that they produce as well as their solution-uptake requirements. For example, when an HPLC separation is employed, the total effluent flow of 1 mL/min can be split into approximately 100 μ L/min to an ESI source while the remainder is injected into the ICP. Because both the elemental profile and molecular identity can be monitored simultaneously, deconvolution techniques might be employed to overcome incomplete separations. In order for such an operation to be successful the output of each source must present the same chromatogram with greatest possible coincidence. Therefore, any convolutions introduced by the splitting operation (through dead volume), any delay time between effluent injection into each source, or any delay in the source itself, must be minimized or characterized. This can be accomplished by injection of a standard prior to analysis of an unknown.

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Ionization Sources:

The preferred embodiment utilizes the ICP and ESI as ionization sources, chosen due to their complimentary nature. The ESI source produces multiply charged molecular ions and molecular fragment ions, permitting chemical structure information to be obtained. The ICP produces principally atomic ions, allowing elemental and isotopic information to be obtained for most elements and with extremely high sensitivity. Simple extension suggests that any combination of sources might be employed as long as they produce orthogonal types of chemical information. For example vaporous samples, such as those from gas chromatography, might be injected into an electron-impact ionization source and the ICP to obtain molecular fragmentation and elemental information simultaneously. Generally, the choice of sources will depend on the value of chemical information obtainable, and the applicable analyte types, mass requirements, and TOFMS operating requirements.

TOFMS

The time-of-flight mass analyzer has several distinct advantages with such a transient system (covered in the response to Question 4 of this disclosure). The invention constitutes a novel TOFMS orthogonal extraction geometry modified to analyze ions produced by two ionization sources ^{or extracted separately} simultaneously. In the preferred embodiment, these sources are oriented 180 degrees from one another and are extracted continuously in opposite directions, as is depicted in Figure 1. Each source has a distinct differentially pumped vacuum interface in order to transfer ions from atmospheric pressure into a vacuum environment (in the case that the sources are atmospheric pressure ion sources). Because each interface region is distinct, it can be tailored to the ion flux and energy produced by the source in question. The ion beams obtained from the two sources are then collimated and introduced into the same extraction region, where they are extracted for mass analysis. Because the ionization sources are oriented in different directions, they attain different trajectories within the drift region of the mass analyzer and, consequently, can be detected separately at different ion detectors. By multiplexing these extraction events sequentially, that is, by extracting the ions from each source in an alternating fashion, both types of chemical information are obtained in a very rapid

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manner. Alternatively, in some cases it might be possible to extract all ions from both sources into the mass analyzer at the same instant.

Redundant Systems:

One key advantage of such a system comes in fusing what would ordinarily be two distinct instruments. The vacuum system, many voltage supplies, and portions of the data acquisition system can be employed simultaneously by both sections of the instrument. The interface regions normally employed with the ICP and ESI have similar vacuum requirements, and thus a single pump can be employed to evacuate the first stage of both vacuum interfaces, and the second and third stages of vacuum served by a single turbomolecular pump, respectively. It can also be seen in Figure 1 that many of the ion optic electrodes are shared by both cycles of the TOFMS operation. If the instrument is operated in a sequential manner, the detection system can be switched rapidly between the two systems, monitoring the output of the ESI detector and ICP detector in an alternating fashion.

Ion Optics:

Because each source is sampled through a distinct interface region, the ion optics responsible for collimating the ion beam prior to its introduction into the extraction region can be tailored to the ion flux and energy of the source in question. For example, when an ESI source is employed, it has been shown that the resulting plume must be dried of excess solvent to attain adequate sensitivity. Further, such a source produces an isoenergetic ion beam of relatively modest intensity, consisting of high-mass ions possessing multiple charges. Thus, the ion optic and extraction system for this source must include a drying region to desolvate ions, and electrodes designed for the appropriate ion energies. These ion optics may consist of novel ion electrodes; for example, Smith and coworkers have employed a modified funnel electrode (6-9). Additionally, many investigators have employed radio frequency multipole ion guides as ion optics in order to collisionally cool the ion beam (10, 11), or a quadrupole ion trap in order to integrate the ion current prior to injection into the extraction region of the TOFMS (12-20). Presumably, either of these systems might be employed within the

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present invention. In contrast, the ICP produces an ion beam of significant intensity and isokinetic energy distribution, consisting of ions of masses limited to the atomic range (roughly 1-250u). Several authors have employed modified electrodes in coupling ICP source to the TOFMS (21). The ability to tailor the ion optic electrodes to the source in question is an advantage of this invention over previous TOFMS arrangements that employ more than a single source in a serial fashion.

TOFMS Parameters:

This instrument is designed based largely on existing TOFMS technology and techniques, but configured so as to sample two different mass ranges of ions from two sources. Thus, a number of possible, known instrument design geometries can be modified to this application. An ion trajectory simulation of a simple design is included as Figure 2 as a means of illustrating general principles and design requirements.

The instrument depicted in Figure 2 is based on the TOFMS geometry generally referred to as "orthogonal extraction" in which ions are extracted into the acceleration region along a direction perpendicular to that of their original motion. Therefore, dependent upon their initial energy they will attain an angle within the flight region according to:

$$\alpha = \tan^{-1} \left(\frac{V_y}{V_x} \right) = \tan^{-1} \sqrt{\frac{E_y}{E_x}} \quad (1)$$

where V_y represents the original velocity of the ions and V_x represents the velocity gained through acceleration (or equivalently, E_y represents the energy of the ion oriented along the y-axis and E_x represents the acceleration energy). If all ions possess the same energy, as is generally the case with the ions produced by the ESI, it follows that all masses will attain the same angle within the drift region and arrive at the same location on the detector surface. This is depicted in Figure 2 for the ions labeled "ESI Ion A" and "ESI Ion B" both of which possess 10 eV of energy ($E_y = 10 \text{ eV}$). Independent of the mass of the ion in question, those extracted from the origin of Ion A in Figure 2 will strike the

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edge of the detector closest to the extraction region, while those of the energy and origin of Ion B will contact the farther edge of the detector. Therefore, the extraction region for that particular source need only be of roughly the same size as the detector to be used (Detector 2).

In contrast, the ICP produces an ion beam with ions having energies with both an isokinetic portion and an isoeenergetic portion, resulting in a primary ion beam trajectory that depends upon mass. Ions of different mass extracted from an identical origin within the extraction region will attain different angles within the flight region, and consequently, strike the detector at different positions. In order to minimize this mass bias, the extraction region must be designed to accommodate a range of ion energies and therefore must be of a much larger size. Figure 2 also depicts two ICP ions (labeled "ICP Ion A" and "ICP Ion B") of differing energy representing the endpoints of the energy window sampled by the extraction region of 10 cm width by a detector (Detector 1) of 4.4 cm diameter.

Another important parameter is the relationship between the time required to refill the extraction region and the time required to complete a mass analysis; this parameter directly dictates the "duty factor" of the instrument and therefore both its efficiency and sensitivity. The repetition rate of the typical TOFMS is limited by the time required for the ion of greatest m/z , and therefore possessing the lowest velocity, to traverse the flight region and strike the detector. When a continuous ionization source is employed, it is also limited by the time required for the incoming ion beam to fill the extraction region in a manner that does not create a mass bias effect. For example, a monoenergetic ion beam sampled by the TOFMS will be under the following restriction:

$$d \leq a \sqrt{2E} \quad (2)$$

where d represents either the detector width along the y-axis or the width of the extraction region (whichever is limiting), a represents the instrument defined proportionality dependent upon the particular instrument (from the flight time relation: $t \propto (m/z)^{1/2}$), and E is the energy of the beam. If the beam contains all masses up to equivalent $m/z = 1000$, it is necessary to delay extraction until that particular mass has filled the extraction region thereby ensuring that the ions extracted are an accurate

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reflection of the composition of the incoming ion beam. Interestingly, there is no mass dependence in equation 3, as the increased flight time with mass compensates for the longer time required to fill the extraction region. For a monoenergetic beam of 10 eV energy and a typical a value of 1.8×10^{-6} , the limiting region size is 8.3 cm.

For an isokinetic ion beam, the situation is different as each m/z is traveling at the same velocity and therefore possesses an energy, E_y , that varies linearly with mass. Accordingly, the size of the region, and therefore the refill time, varies with the mass range under investigation. Because each mass possesses a different energy, extraction must be delayed until the range of m/z in question has had enough time to pass to the appropriate position within the extraction region from whence it can strike the detector surface. The time required to refill the extraction region is fundamentally linked to the mass range under investigation, and can be calculated as:

$$\text{Refill Time} = a \left(\sqrt{\left(\frac{m}{z} \right)_{\text{HIGH}}} - \sqrt{\left(\frac{m}{z} \right)_{\text{LOW}}} \right) \quad (3)$$

where m/z_{HIGH} represents the greatest m/z to be sampled and m/z_{LOW} the smallest m/z under investigation. It is interesting to note that the refill time, and thus the repetition time limit, is independent of the velocity of the incoming ion beam and dependent only on the acceleration of the instrument. For a typical ICP-TOFMS mass spectrometer, the mass range of interest would be from $m/z = 2$ to $m/z = 250$, with the maximum repetition rate ($1/\text{Refill Time}$) would be 39 kHz. For comparison, the maximum repetition rate dictated by the flight time would be 35 kHz.

In a situation in which the ion beam of interest has properties of both isokinetic and monoenergetic production (which exists, for example, with the ICP), the situation becomes more complex. Because the beam contains aspects of both isokinetic and monoenergetic beams, the refill time and dimensions are dependent on the mass range (from M_{HIGH} to $M_{m/z}$), on the detector size (DETECTOR), on the offset potential (E_0), on the expansion temperature (T), and on the TOF parameter (a). The refill time can be calculated from the relation:

$$\text{Refill Time } (M_{m/z}) =$$

$$\begin{array}{c}
 \text{DETECTOR} + a\sqrt{Avq} \left[\frac{\sqrt{5M_{\text{HIGH}}kT + 2E_0M_{\text{Ar}}q}}{M_{\text{Ar}}q} - \frac{\sqrt{5M_{m/z}kT + 2E_0M_{\text{Ar}}q}}{M_{\text{Ar}}q} \right] \\
 \left[\frac{\sqrt{5M_{m/z}kT + 2E_0M_{\text{Ar}}q}}{M_{\text{Ar}}M_{m/z}} \right]
 \end{array} \quad (4)$$

where M_{Ar} represents the mass of argon (the bath gas in this case), k is the Boltzmann constant, q is the elemental charge, and Av is Avagadro's number. The m/z possessing the limiting refill time changes depending upon the relative magnitudes of the temperature and offset potential, but will always be less than that dictated by the isokinetic expansion case.

All TOFMS instruments attempt to compensate for the initial spatial distribution of the ion packet, and thus minimize the errors in flight time. Overwhelmingly, this is currently accomplished by space focus techniques that are well known within the literature. Because the space focus plane location is independent of m/z , a single set of instrument conditions will suffice for both ion sources. Under conditions in which the field strengths within the extraction and acceleration regions (a_1 and a_2 in Figure 2) are of equal magnitude, the second-order primary space focus plane will be located at a distance $a_1 + 2a_2$ from the end of the acceleration region. In considering other extraction region geometries, it is necessary to retain these space focus conditions.

Time of flight instruments also employ energy compensation techniques, such as an ion mirror, in order to compensate for the distribution of initial velocities among the ions that are extracted. The degree to which these errors are compensated for is often expressed in terms of the reduced flight time difference ($\partial t/T$) as a function of acceleration potential defect ($\partial U/U$). Given that, under most conditions, the ions from the different sources experience the same acceleration potentials, it is possible to use the same reflectron configuration for both ion sources. If the extraction regions of the ions from the two sources are different, and in some cases in which they are identical, it may be advantageous to employ two distinct reflectrons. It is noteworthy that it is possible to employ the reflectron as a means of increasing the a factor, and thereby the offset distance of the masses.

Two measures of efficiency might be quoted for this instrument: the duty cycle relating to the analysis of ions produced by each single source, and the source partition ratio pertaining to the fraction of the analysis time pertaining to each source. The duty cycle as it refers to each source is defined by:

$$DutyCycle = \frac{f_{SOURCE} d_{SOURCE}}{Vel_{SOURCE}} \quad (5)$$

where f_{SOURCE} represents the number of extraction events for that source per second, d_{SOURCE} represents the extraction region width, and Vel_{SOURCE} represents the average velocity of the ions in the primary (pre-extraction) beam produced by that particular source. If gating is employed, the duty cycle reduces to the product of the TOFMS frequency and the modulation gate pulse width, but remains limited in the maximum by Equation 5. Further, a source partition ratio can be defined to represent the segregation of the available analysis time between the two sources. For example, a ratio of 3:1 would represent 3 extraction events from source 1 for every one from source 2.

Extraction Region Geometries, Extraction Sequences, and Ion Gating:

Figure 3 illustrates several potential extraction region geometries that might find use within the invention. Because there exist several permutations of existing extraction region designs there also exist a large number of possibilities that fall within the design guidelines outlined above. Here, we define the extraction region loosely as the space contained between the repeller (R) and the first acceleration electrode (G1). Ions are extracted for mass analysis by application of a voltage pulse (V_R) to one or both of the electrodes. Again, the simplest form shown in panel A in Figure 3 projects both ion beams along the same axis, but traveling in opposite directions. Here, a single extraction pulse might inject ions from both sources into the acceleration region. As the ions fall through the same potential gradient, the ion energy distributions of these populations will be identical and therefore many of the same ion optics and reflectron potentials might be employed for both sources.

Alternatively, the beams might be spatially offset along the x-axis (i.e. along the direction of the flight tube) within the extraction region, as is depicted in panel B in

Figure 3. Because the beams are not coaxial, any difficulties arising from space charge effects, the collisions of ions from one source with those of the other, or collisions of ions with the neutral beam of atoms created by the sampling process are overcome. Both populations of ions are subjected to the same field upon extraction; however, because the initial position of each population is different, each possesses a different spatially dependent energy. While the space-focus plane position remains the same for each case, the ion optic and reflection potentials may be slightly different. In panel C in Figure 3, the ion beams are vertically offset. In the limit, because the beams are vertically offset, one might create completely separate extraction regions for both sources.

Finally, Panel D illustrates a two-extraction region design wherein each ion beam is injected into a separate extraction region. In Figure 3, Source 2 is injected into the negative injection region. When an extraction is required, a negative repeller pulse is applied to the grid R- and the ions are pulled in to the acceleration region. Conversely, Source 1 is injected into the positive extraction region, when a positive potential is applied to the repeller R+ while the negative potential is also applied to the negative repeller R-, these ions are injected into the acceleration region. In this way, the electric field gradient remains constant throughout each extraction region and space-focus conditions are thus satisfied. Here, the space focus plane will be in a different position for each ion population, and reflectron and ion optic conditions will be necessarily different. Obviously, there exist many permutations of these basic geometries.

In every case, extraction from the two sources might be accomplished in a sequential or simultaneous fashion. When the ions from both sources are injected simultaneously into the TOFMS, the repetition rate of the instrument will be limited by the lesser of the attainable repetition rates for the two particular sources, which, according to the previous discussion, is dependent upon the mass ranges in question, the ion beam energies, and the extraction region size. As an illustration, consider an ESI/MCP instrument of parameters similar to those discussed above, possessing an extraction region similar to the types shown as A, B, or C in Figure 3. A pictorial description of the timing sequence of such a system is given in Figure 4 in the form of a modified bar diagram with the duration of each step in the repetitive sequence scaled in the horizontal direction of increasing time, and the vertical dimension representing different spectra.

Examples include systems with segmented extraction regions (Figure 1) and segmented reflection (Figure 5).

6/

SECRET

7/

ESI ions fill the extraction region while the ICP ions are undergoing mass analysis. The process then repeats itself.

References: All of which are incorporated herein by reference.

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20010-123456789

What is claimed is:

1. A method of acquiring chemical information with a mass spectrometer having (i) a first ionization source for creating ions, (ii) a second ionization source for creating ions, (iii) a first detector for detecting ions, and (iv) a second detector for detecting ions, comprising:

(a) simultaneously sampling ions created by said first ionization source and said second ionization source so as to produce a first ion sample and a second ion sample; and

(b) simultaneously detecting ions from said first ion sample with said first detector and ions from said second ion sample with said second ion detector.

20250101-162454

INVENTION DISCLOSURE INVENTION DESCRIPTION

(Attach additional sheets as necessary.)

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1. Describe the particular problem the invention seeks to solve.

It is well recognized within the scientific community that metals play a critical, but currently indefinite, role in a myriad of biochemical processes and are therefore of critical importance in such fields as environmental monitoring, pharmaceutical research, and medicinal chemistry. At present, there exists no single, integrated means of determining the complete speciation information of a metal within a sample.

Here, speciation is broadly defined as the chemical form that the specific metal takes within the sample, defined, for example, by the different oxidation states of the metal or the forms complexed or bound to inorganic and organic matter. The function of this invention is the rapid acquisition of such information from complex mixtures of environmental, biological, or pharmacological interest to be employed for screening, unambiguous detection of target species, or generally when analyses requiring knowledge of both elemental and speciation information are necessary.

2. Describe previous attempts to solve the problem and the limitations or deficiencies your invention overcomes in the state of the art.

State of the art analyses are currently accomplished by the successive, separate acquisition of elemental and metal-speciation information taking the general form of a mixture separation followed by analysis for elemental or speciation data. For example, a mixture might first be subjected to separation by liquid chromatography and the effluent analyzed for metals by inductively-coupled plasma mass spectrometry; the identical mixture separation is again accomplished and the effluent analyzed for speciation data by electrospray ionization mass spectrometry. In order to compare these two separations, and thereby determine the concentration and identity of metal-associated species within the mixture, peak retention-time matching is necessary and the analysis is thereby open to associated error due to separation inconsistencies.

Further, this procedure is necessarily somewhat inefficient as it requires two separate instruments. It is therefore costly, is inefficient in its use of analyte, and cannot be accomplished in a timely manner.

This invention monitors both types of information with each single separation. Thus, the analysis is free from error due to run-to-run variations and the identity of metal-containing species can be accomplished by direct comparison. Because the elemental identity and metal speciation data represent orthogonal types of information, the incomplete separation of components in a mixture can be overcome by deconvolution techniques. Finally, as this invention embodies a single instrument, analysis are completed more efficiently and rapidly with less associated cost.

3. Please attach a complete description of the invention (*the detail should be similar to that of the methods and results sections of a publication*). This description may be by reference to a separate document (*copy of a report, preprint, grant application, or the like*). If so, give a brief summary below and attach the document to this disclosure.

See Attached Description

4. Describe the novel features of your invention and why they are significant.

INVENTION DISCLOSURE

This geometry is novel in that the desired chemical information is acquired from the sample simultaneously, with a single instrument, and from a single separation as opposed to the current serial means employing several instruments. This TOFMS instrument geometry is unique in design and capabilities. Several advantages of this invention issue from the particular use of a time-of-flight mass spectrometer as the fundamental instrument platform. As many of these advantages are well recognized within the literature, they will be only briefly mentioned here. Time-of-flight mass spectrometers are capable of extremely rapid mass-spectral acquisition, allowing the rapid transients produced by the separation to be completely characterized. Because all of the masses are extracted to be analyzed at the same instant, TOFMS is recognized to be unaffected by spectral skew error, or the error associated with the scanning acquisition of mass-spectral data during the time-dependent concentration profile of a transient signal. Such a limitation would significantly impair the effective use of a scanning mass spectrometer in this application. Further, the simultaneous extraction of all masses of interest allows greater precision to be attained in ratioing techniques, such as isotope dilution or internal standardization.

These advantages make such an instrument potentially very useful in the complete characterization of extremely complex mixtures and with systems producing extremely rapid transients. One appropriate example might be the rapid screening of combinatorial libraries.

This TOFMS geometry is unique in its ability to rapidly interdigitate the acquisition of the two distinct types of chemical information from two distinct sources. This fact alone distinguishes it from TOFMS instruments based upon prior art. Such an application requires the observation of two substantially different mass-to-charge ranges with large dynamic range and with high temporal resolution. The use of this TOFMS geometry permits the simultaneous, or rapidly alternating, acquisition of the data from the two distinct ionization sources under investigation.

This ability is largely a consequence of the rapid spectral generation rate of the TOFMS and the fact that the instrument employs electric fields that can be rapidly changed. This novel TOFMS geometry also allows modification of the duty cycle with which each source is monitored. For example, an ESI source, being a weaker source, may take up a greater portion of instrument acquisition time in order to present each source with similar signal-to-noise ratios.

This invention represents the integration of the capabilities of two distinct instruments wherein each type can be utilized separately to full advantage, or combined to realize the aforementioned additional advantages. Such an instrument is less costly to construct since several components, such as vacuum pumping, are redundant and sections of others, such as portions of the electronics and detection systems, can be greatly integrated. Furthermore, the proposed geometry allows the use of ion optical elements optimized for the ion current and ion energies produced by each distinct source, allowing greater sensitivity to be achieved as compared to a single, compromising, ion optics system. In effect, this embodiment possesses all of the advantages of previous instrumentation within a single instrument.

5. Describe the state of development (*prototype, animal model, other research results*).

Currently, the instrument is in the final design stages. This laboratory has significant expertise in the design, construction, and operation of both ICP-TOFMS and ESI-TOFMS instruments.

6. Are there other contemplated forms of the invention or alternate aspects and uses?

VENTION DISCLOSURE

Use of an additional, orthogonal detector system (ultraviolet absorption or fluorescence, for example) in-line prior to the analysis of the effluent by the aforementioned instrument would permit further information to be gained and facilitate analysis of mixtures that are not completely separated by the chromatographic step. This TOFMS design will also be able to use other sources capable of providing different types of information, such as matrix induced laser desorption or microwave plasmas. In principle, any number or type of sources capable of providing orthogonal information about a chemical sample might be employed. One additional capability that would provide even more information would be the addition of a collision induced dissociation cell in order to fragment ions further, to simplify their subsequent identification. Finally, the addition of an quadrupole ion trap as a integrating device along the ion chain would further improve duty cycle and thereby sensitivity.

202010-145545

P224 NEW KNOWLEDGE AND INSTRUMENTATION FOR PLASMA-SOURCE MASS SPECTROMETRY. Gary M. Hieftje, James H. Barnes, IV, Gerardo Gamez, Ole A. Grøn, Mao Huang, Scott A. Lehn, Denise M. McClenathan, Steven J. Ray, William C. Wetzel, Department of Chemistry, Indiana University, Bloomington, IN 47405; M. Bonner Denton, Department of Chemistry, University of Arizona, Tucson, AZ 85724, and David Koppenaal, Pacific Northwest National Laboratory, Richland, WA 99352

Plasma-source mass spectrometry, most commonly implemented as ICPMS, has evolved into a widely used routine tool for ultra-trace elemental analysis. The technique offers detection limits at the ppq level, modest precision (1-5% RSD), reasonable levels of matrix and spectral interferences, broad dynamic range, and relative ease of use. Given this situation, it is therefore appropriate to question whether additional dramatic changes in the methods seem likely in the future. In this presentation, several fundamental investigations and instrumental developments will be discussed that suggest important developments still lie ahead.

The fundamental investigations will center on the measurement of fundamental ICP parameters (electron number density, electron temperature, and gas temperature) and of species introduced with the sample solution (both analyte species and concomitants) in an effort to clarify the effect of the ICP sampling interface on the plasma. Recent studies in our laboratory have shown that the interface has a substantially greater impact on the plasma than was previously believed. These continuing investigations are aimed at determining whether the changes are of the result mainly of thermal losses from the discharge or rather are due to interception of radiofrequency power by the sampling cone.

Instrumental developments will include recent studies into our array detector atomic mass spectrometer (ADAMS), new approaches that employ a time-of-flight mass spectrometer (TOFMS) and the use of alternative sources. Development of ADAMS has continued, and figures of merit obtained from alternative sources (ICP, glow-discharge, and microwave plasma torch) will be compared. In addition, performance of the instrument with a new multi-channel detector array will be evaluated. Unlike previous similar arrays, the new one employs Faraday cups for detection coupled with a chip that enables either destructive or non-destructive readout to take place. Moreover, individual pixels on the array can be randomly accessed, so dynamic range can be maximized for each channel independently. Already, the array has demonstrated the detection of as few as 10 ions.

ICP-TOFMS studies that will be described include one that is oriented toward clarifying the role of operating frequency of the ICP. The LECO Renaissance instrument is capable of operating at either 27.12 or 40.68MHz; however, no definitive study has yet been performed to determine which of the two operating frequencies is better. Another study that will be briefly described includes the coupling of hydride generation with ICP-TOFMS and the potential utility of capillary electrophoresis for speciation of elements amenable to hydride generation.

Lastly, a new instrument for speciation will be introduced. Unlike past efforts that have been made both in our laboratory and in others, speciation in this new instrument is accomplished not

by means of a single tunable or switched source, but rather by two separate ion sources introduced into the same mass spectrometer. Because two kinds of spectra (atomic and molecular) can be obtained in a truly simultaneous fashion, this new instrument offers unparalleled information-gathering capability and should be powerful especially when combined with separation techniques.

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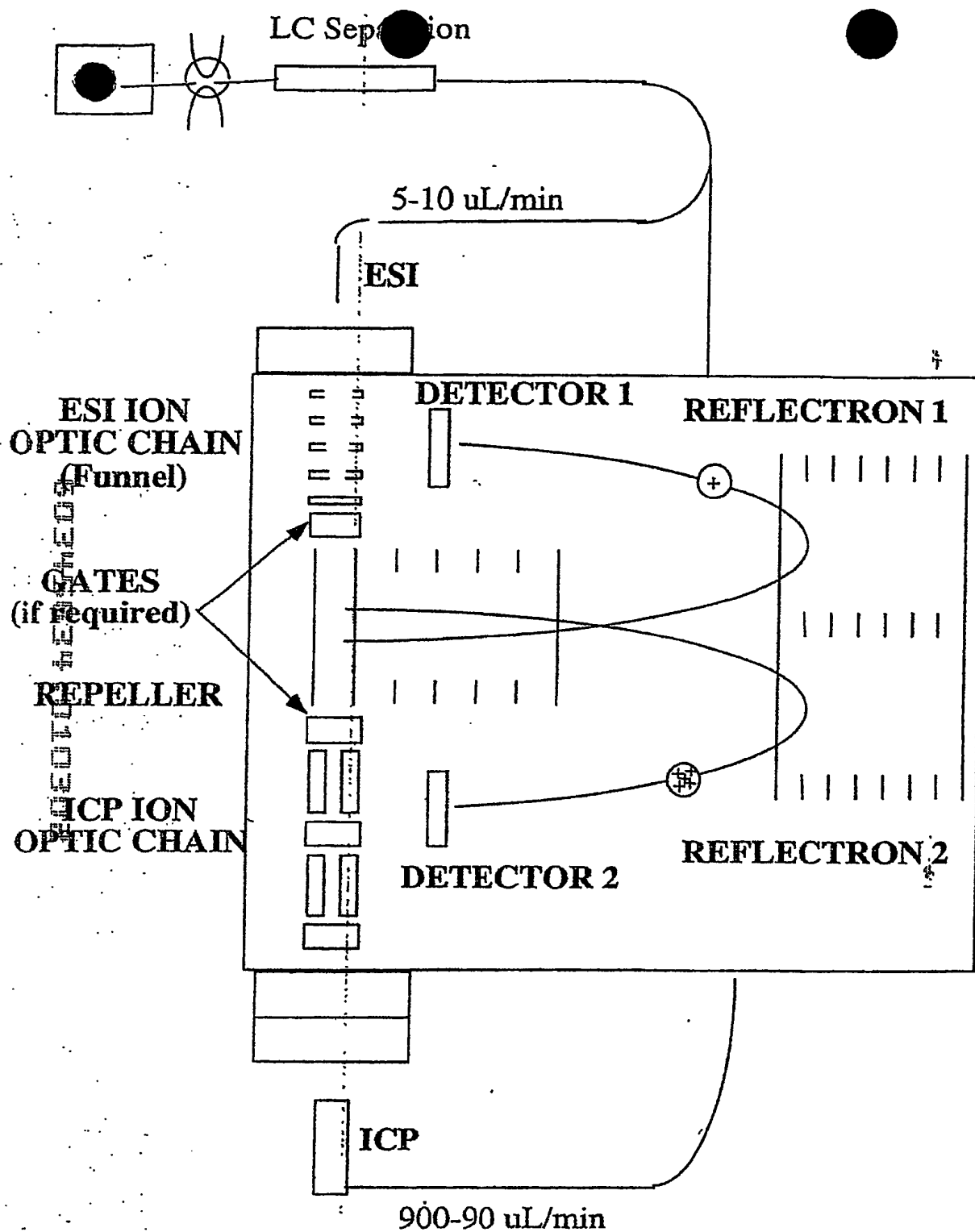


Figure 1: ESI/ICP TOFMS Instrumental Concept

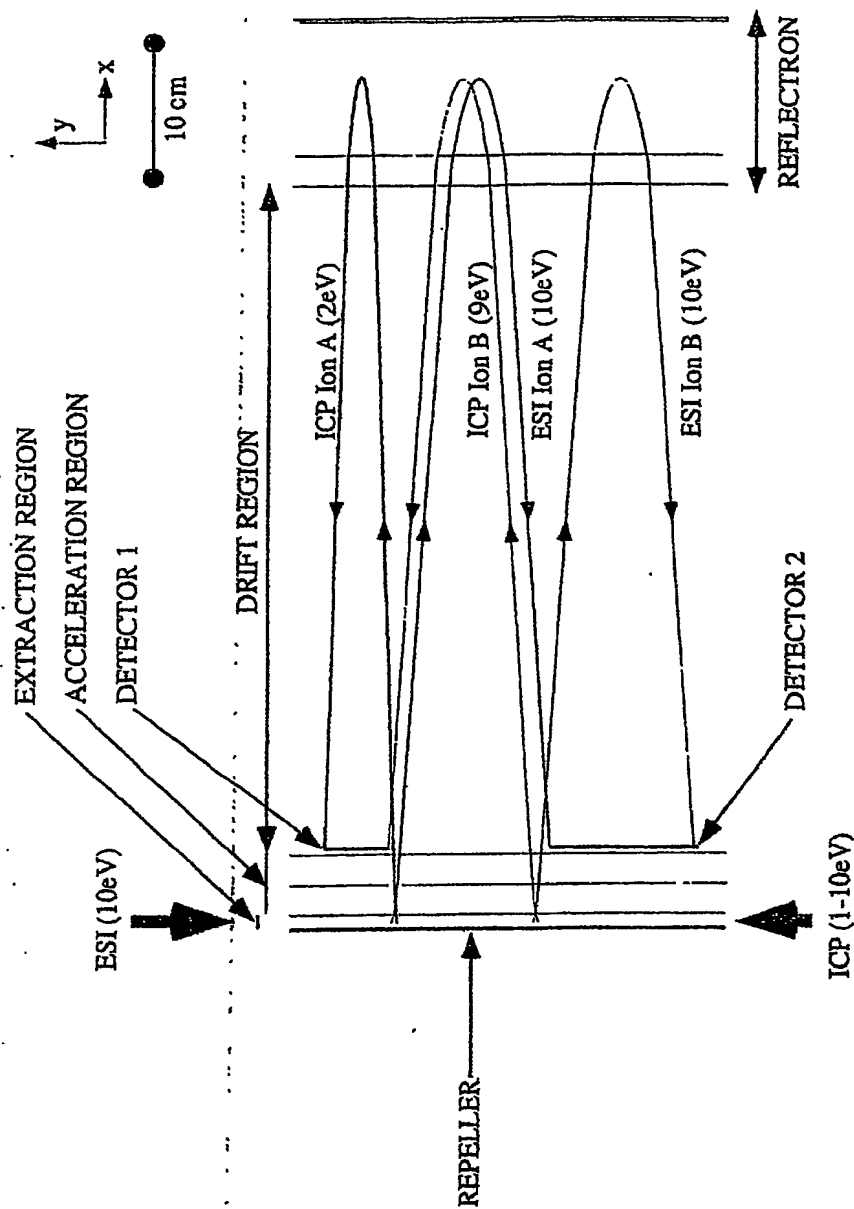


Figure 2: Ion Trajectory simulation of dual source ESI/ICP TOFMS. Ion trajectories of both the isokinetic ions produced by the ICP and the isoenergetic ions produced by the ESI are depicted.

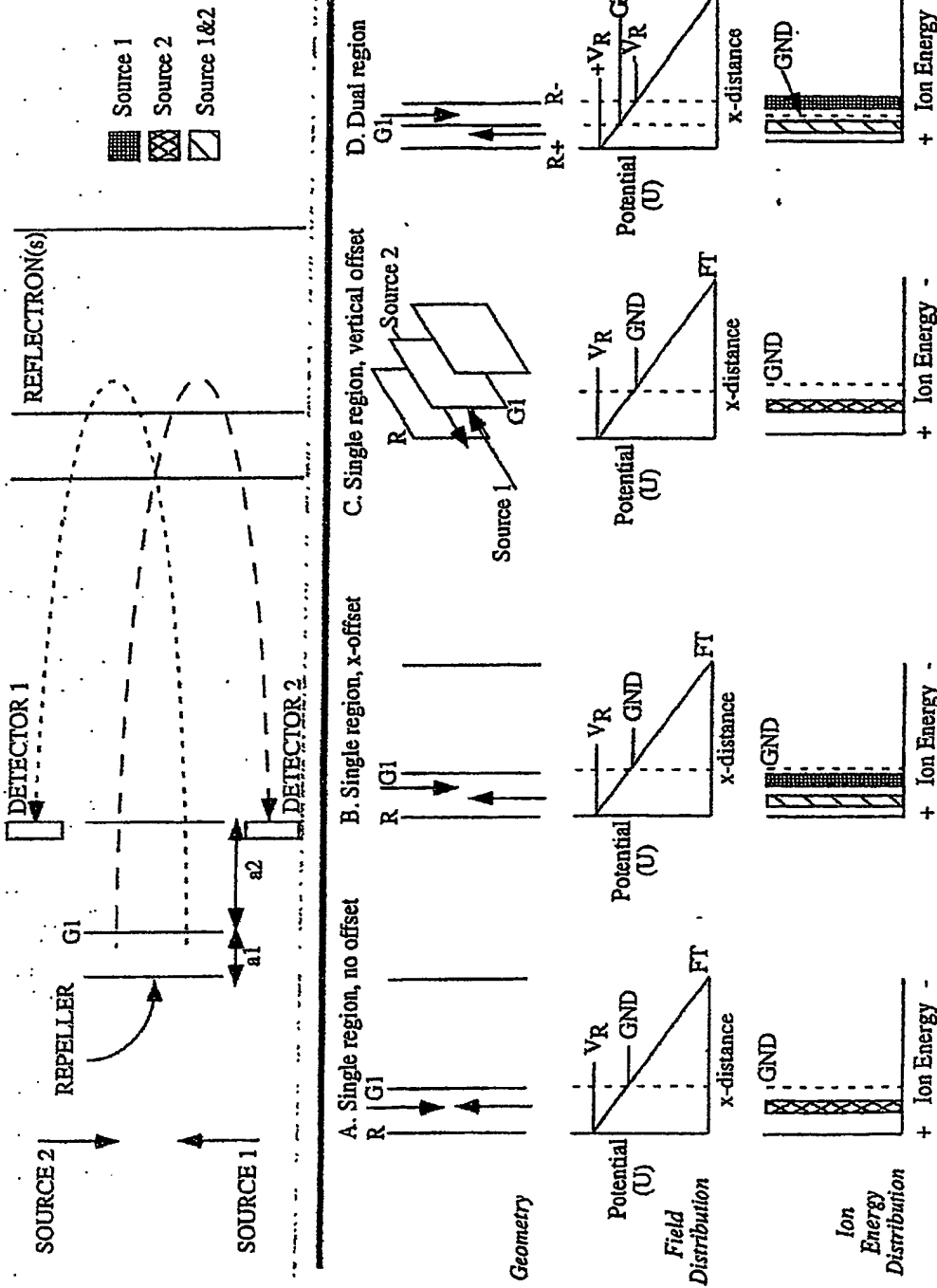


Figure 3: Extraction region geometries, electric field distributions, and ion energy distributions. R-Repeller, G1- First acceleration electrode, VR - extraction potential, FT - Flight Tube Potential, a1 - extraction region, a2- acceleration region.

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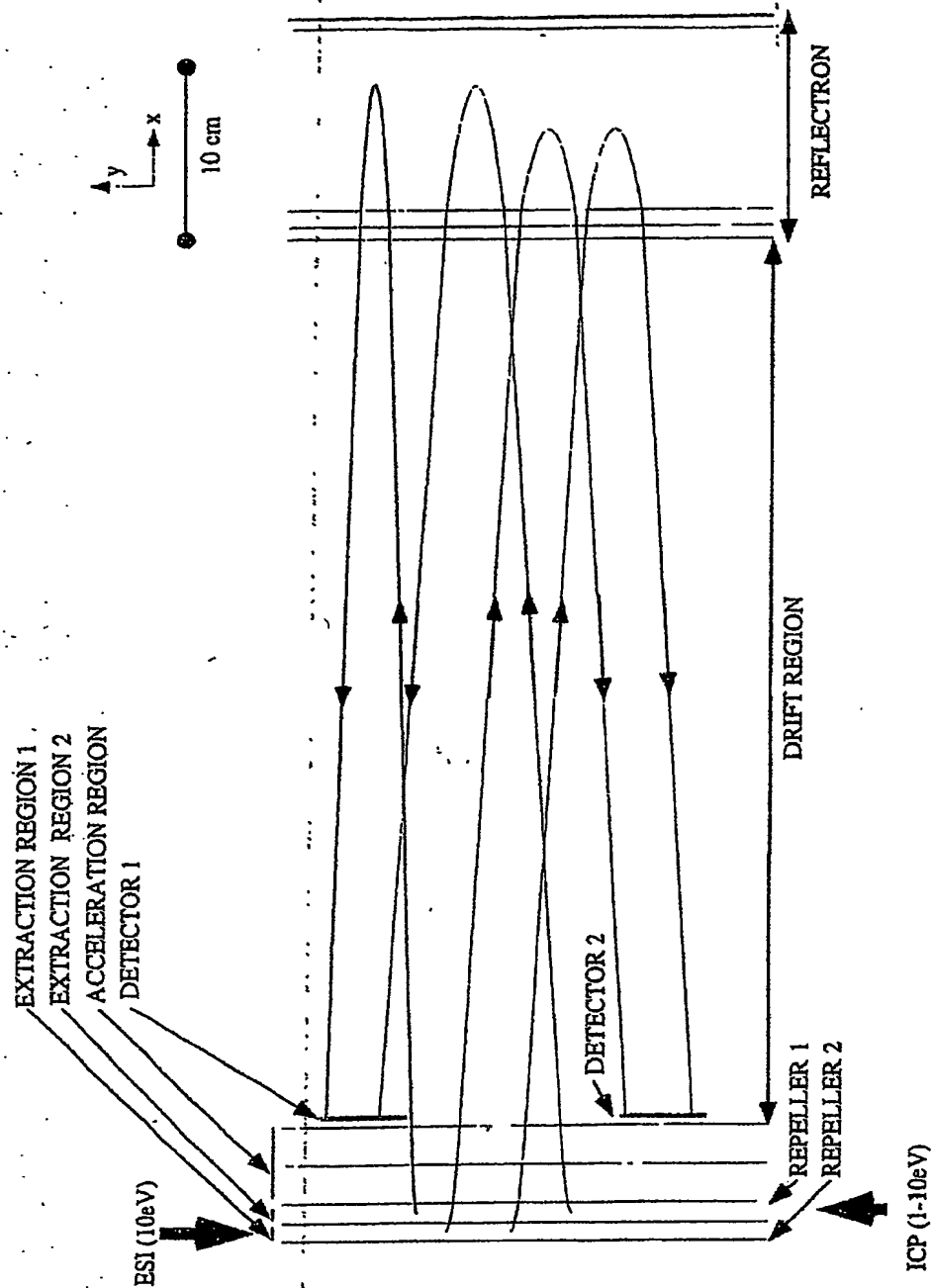


Figure 4: Ion Trajectory simulation of a dual source ESI/ICP TOPMS with a segmented extraction region shown during a simultaneous extraction cycle. Ion trajectories of both the isokinetic ions produced by the ICP and the isoenergic ions produced by the ESI are depicted.

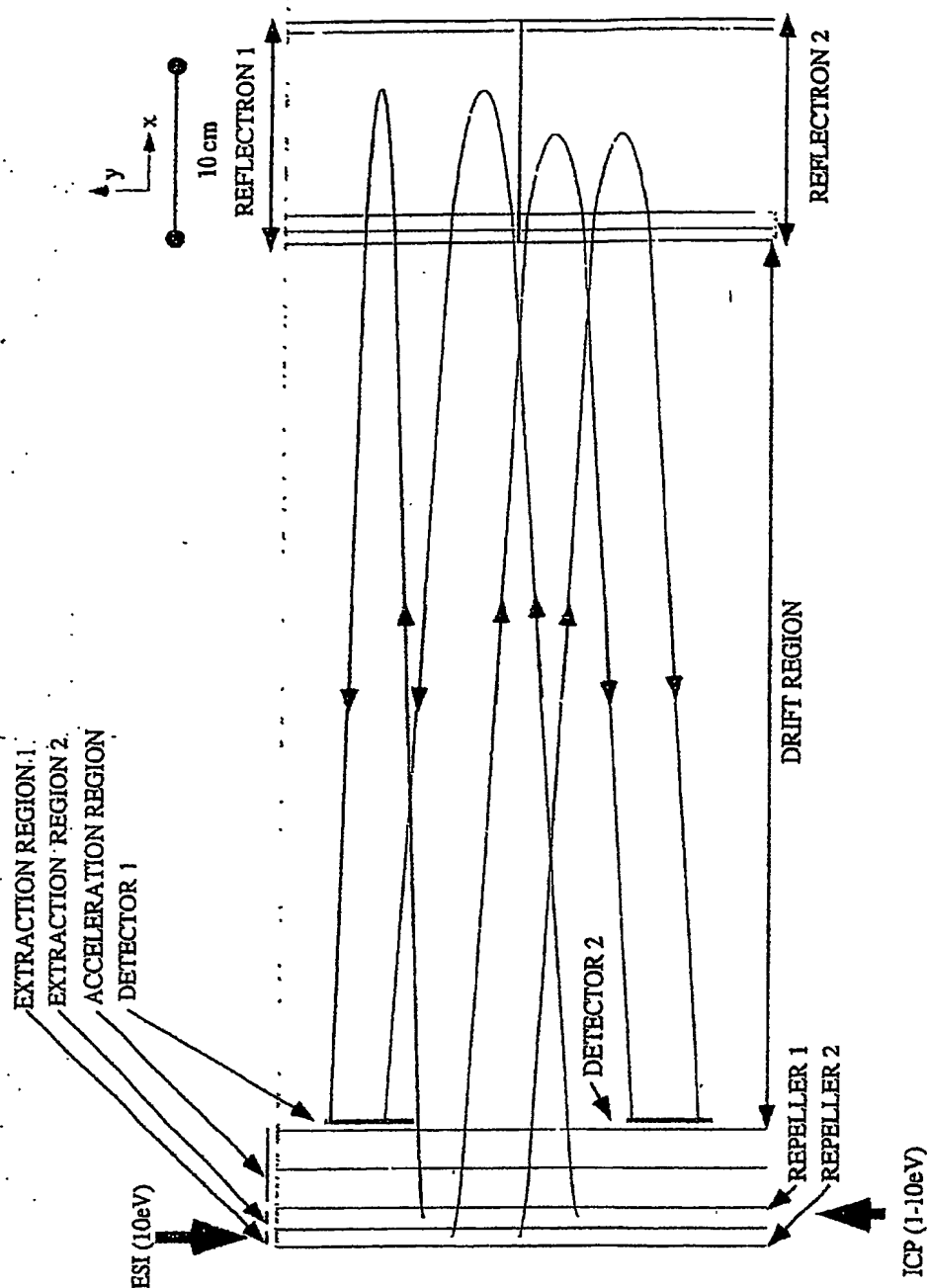


Figure 5: Ion Trajectory simulation of a dual source ESI/ICP TOFMS with a segmented extraction region and segmented reflectron shown during a simultaneous extraction cycle. Ion trajectories of both the isokinetic ions produced by the ICP and the isoenergetic ions produced by the ESI are depicted.

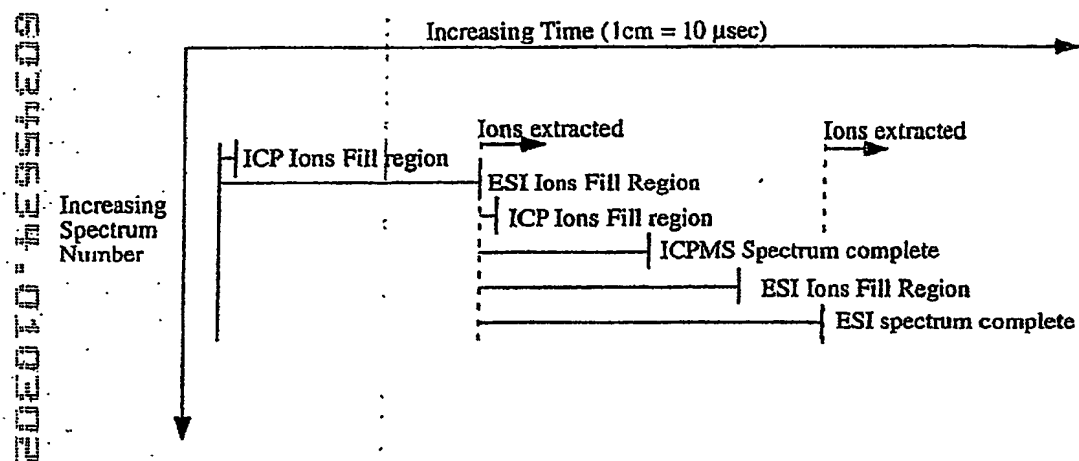
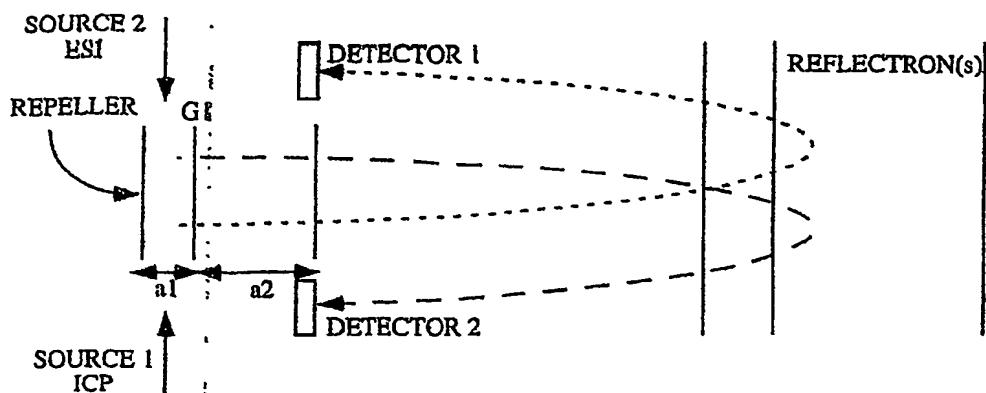
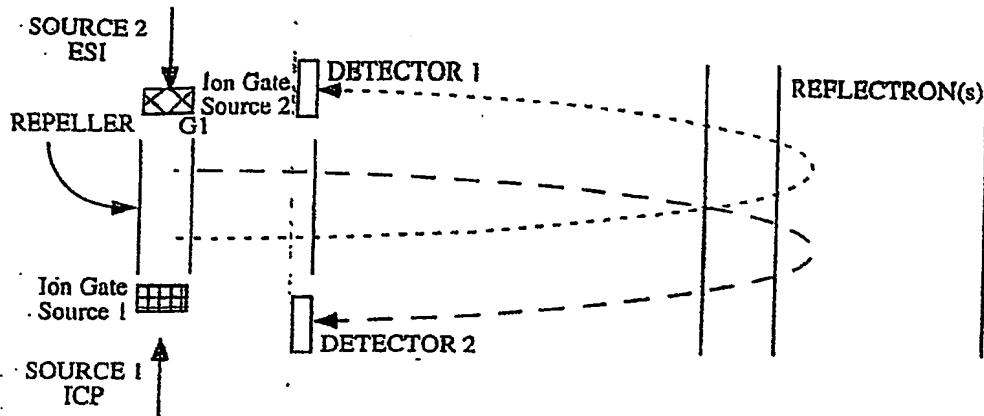


Figure 6: Timing sequence for a simultaneous extraction ESI/ICP TOFMS instrument.



Increasing Spectrum Number

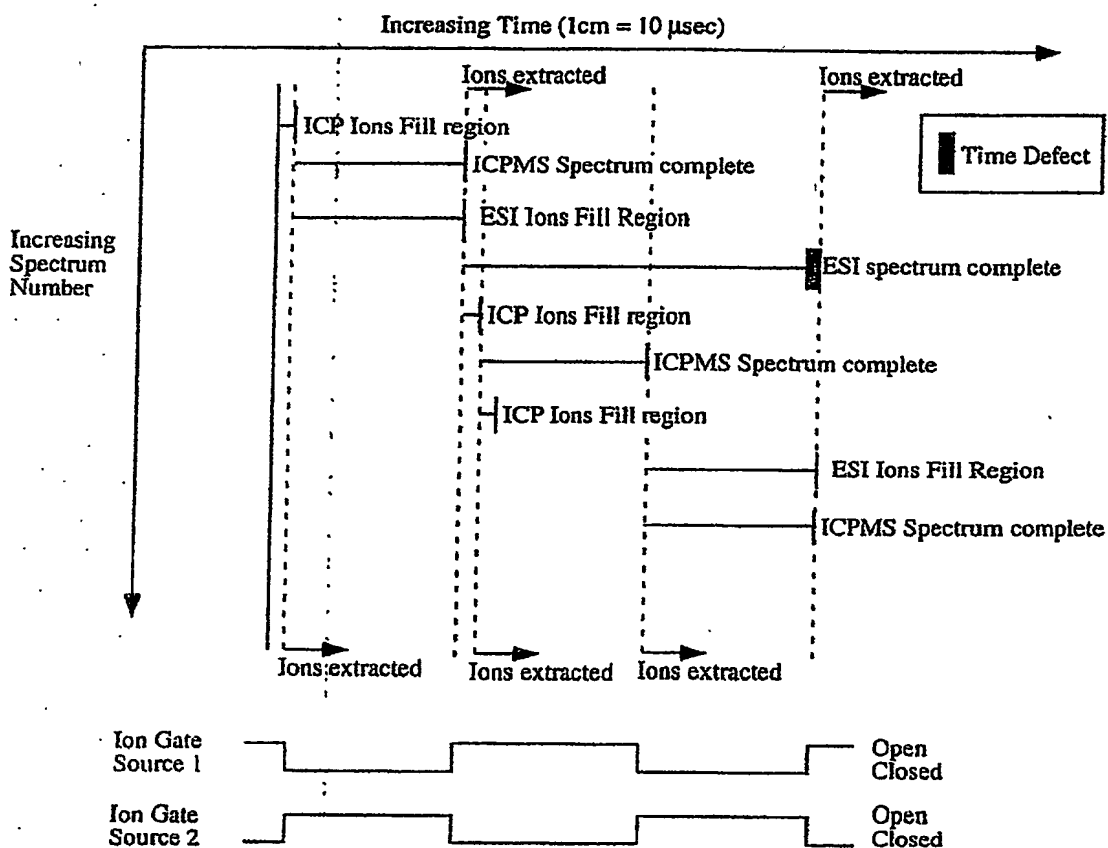


Figure 7: Timing sequence for a sequential, gated ESI/ICP TOFMS instrument.

New Knowledge and Instrumentation for Plasma-Source Mass Spectrometry

G.M. Hieftje, J.H. Barnes, G. Gamez,

O. Grøn, M. Huang, S.A. Lehn,

D.M. McClenathan, S.J. Ray, W.C. Wetzel,

M.B. Denton, D.W. Koppenaal

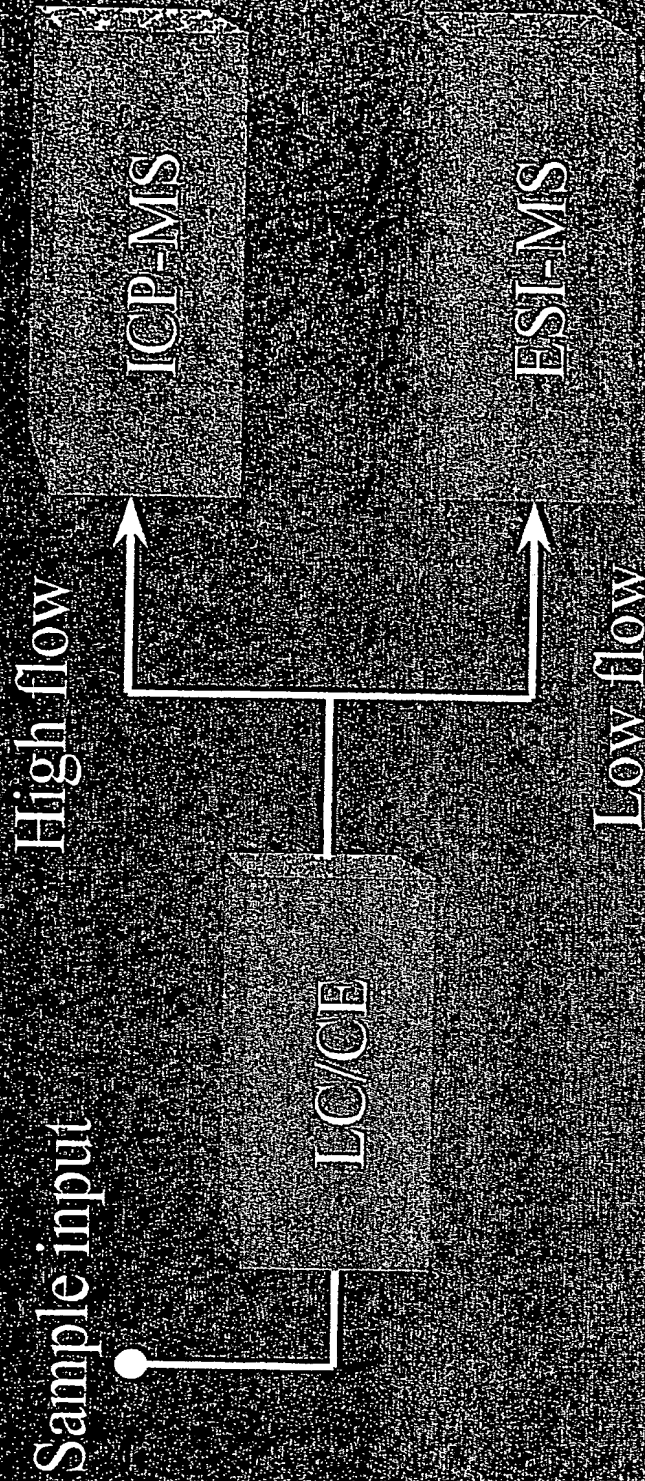
Why PS-MS for proteomics?

- Roughly 30% of all proteins contain heavy atoms (usually metals)
- Important to ascertain which proteins contain metals, which metals they contain, and whether more than one metal is there
- PS-MS affords high sensitivity, speed
- PS-MS might give total elemental composition (C, H, N, S, Metals)

PS-MS in proteomics: questions

- Which plasma source? ICP?
- A second source? (e.g. ESI)
- Which mass spectrometer?
- In conjunction with which other methods?
 - ◆ Which separation technique?
 - ◆ Parallel or serial?

Metal Proteomics: Approach #1



Features of Approach #1

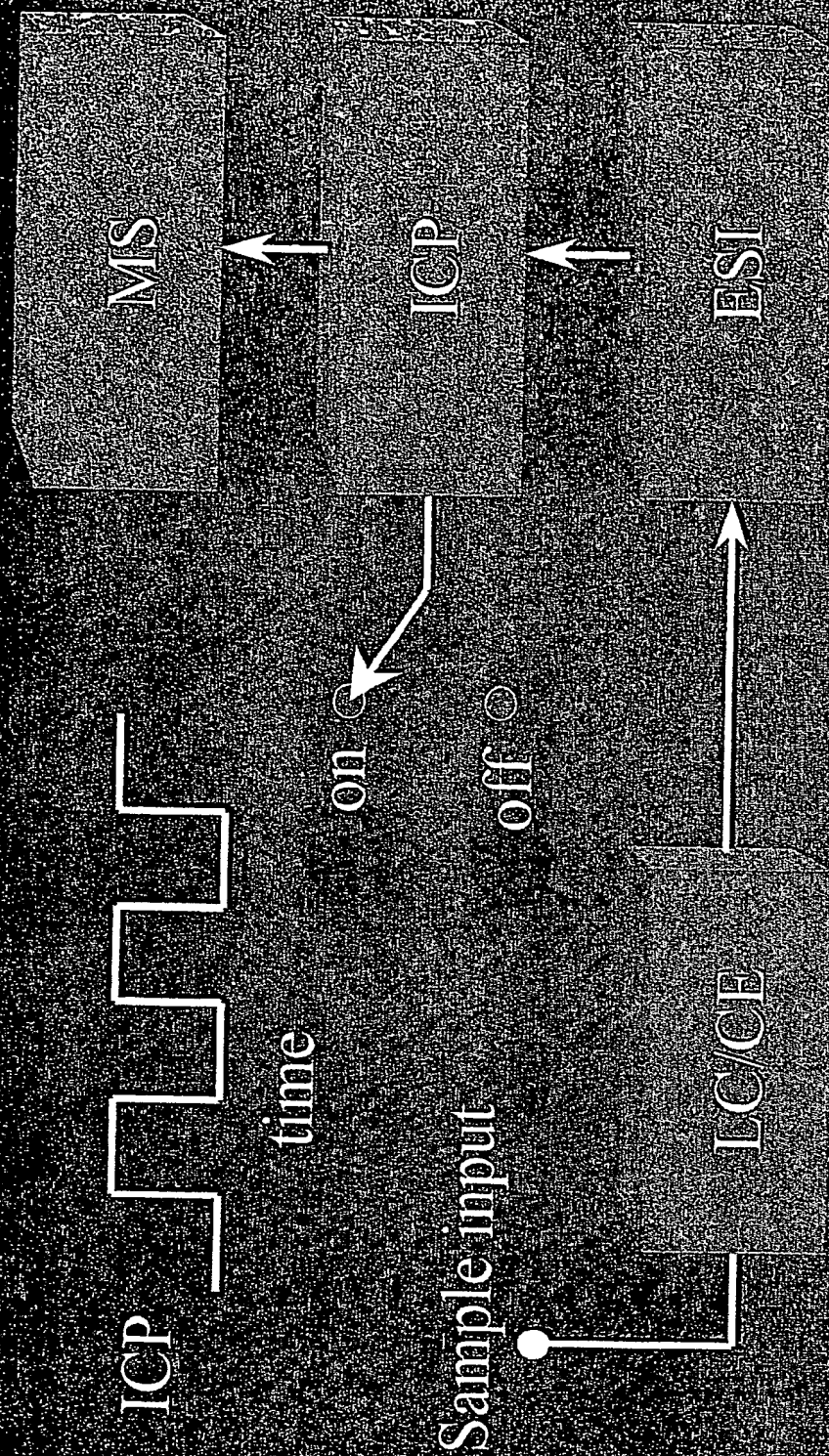
■ Advantages

- ◆ Off-the-shelf
- ◆ Flexible (tailor MS to individual source)

■ Shortcomings

- ◆ Expensive
- ◆ Timing, correlation problems

Metal Proteomics: Approach #2



Features of Approach #2

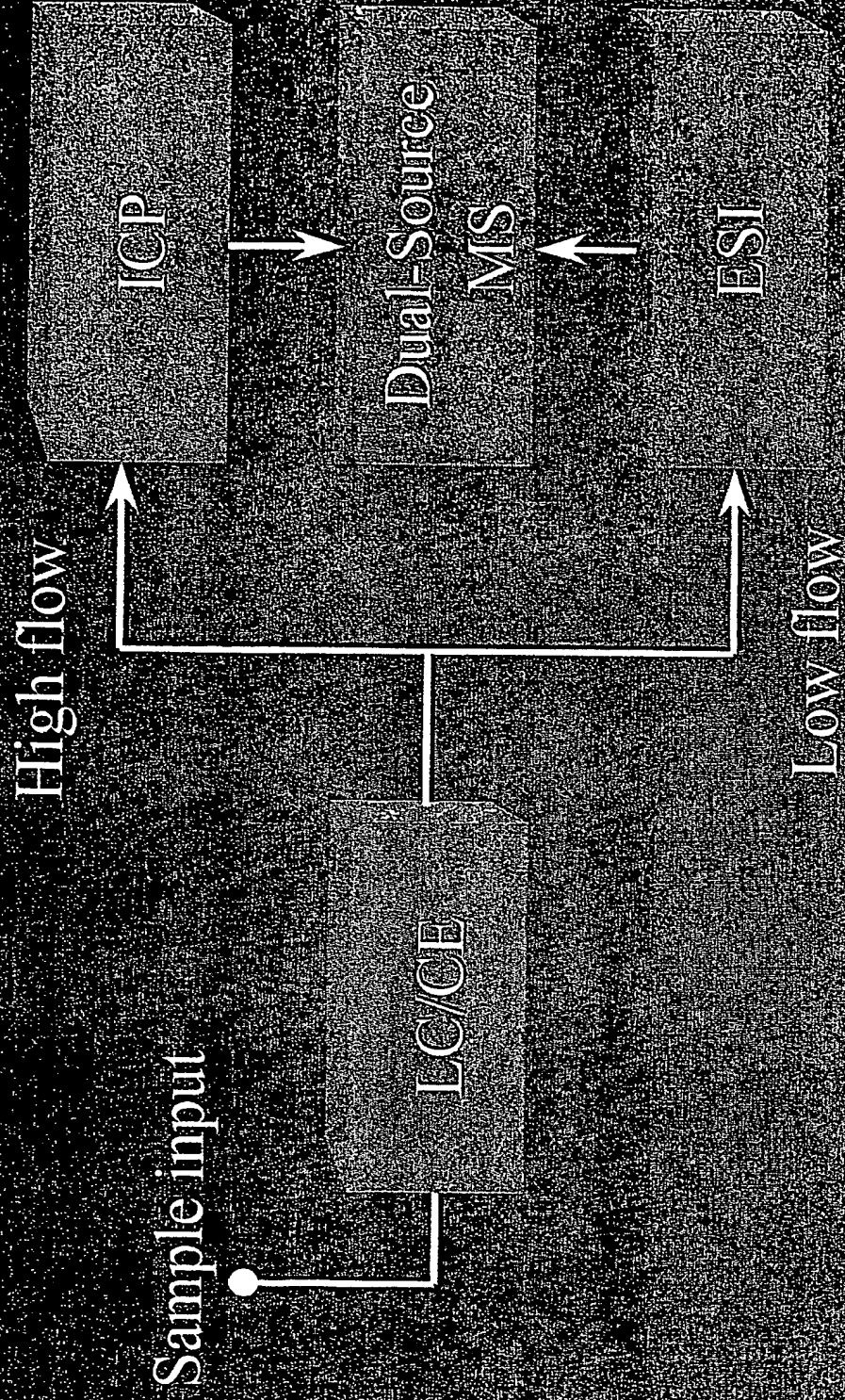
■ Advantages

- ◆ Timing/correlation problems eliminated
- ◆ Only one MS required

■ Shortcomings

- ◆ “Off” time of ICP is limited to $\sim 50 \mu\text{s}$ without re-ignition. Re-ignition is too slow.
- ◆ Duty factor; only one source at a time
- ◆ Requires fast MS
- ◆ Unproven combination source (ESI-ICP)

Metal Proteomics: Approach #3



Features of Approach #3

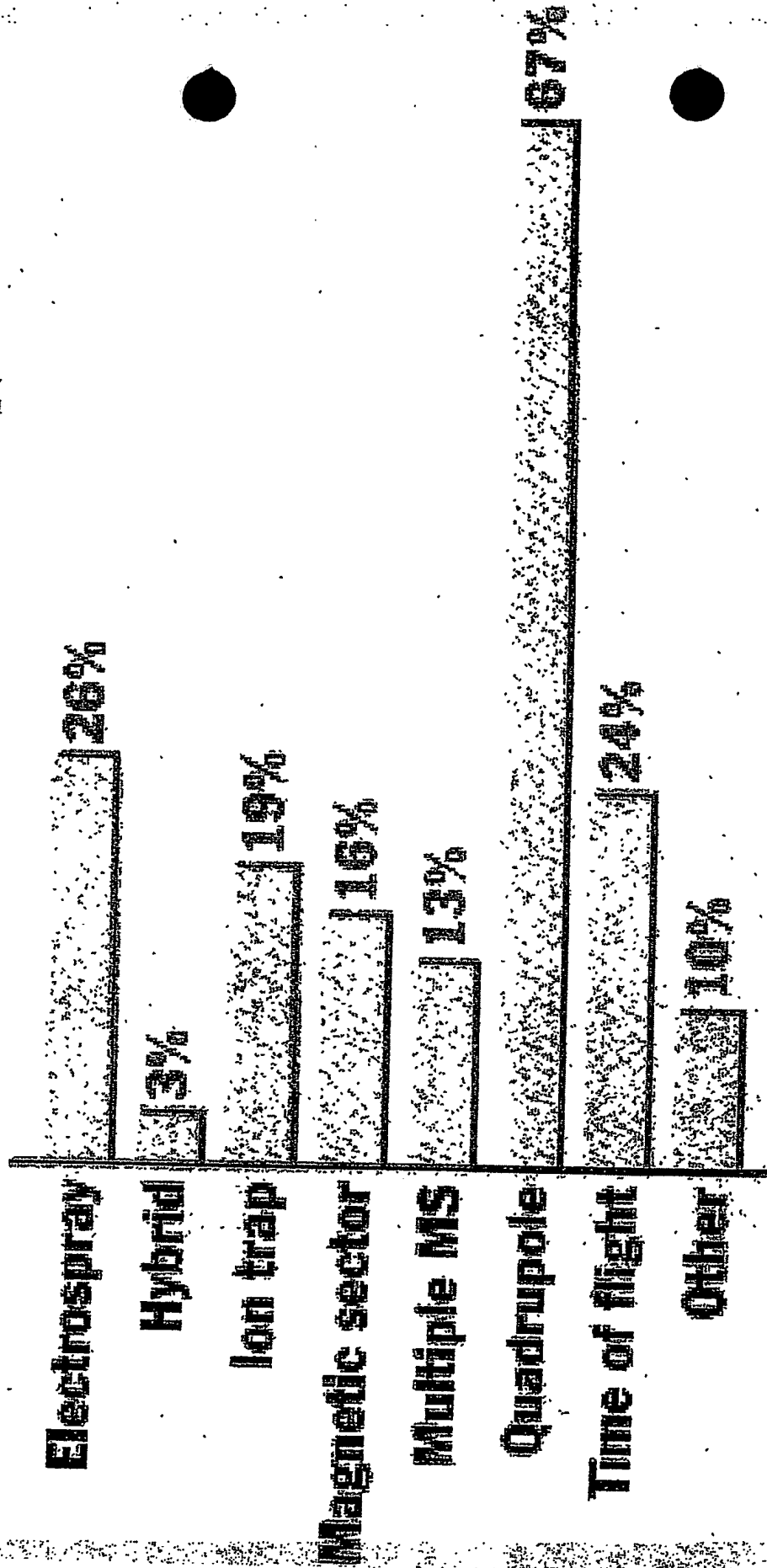
■ Advantages

- ◆ Only one MS required
- ◆ Timing/correlation problems lessened
- ◆ Can use existing sources
- ◆ Unity duty factor

■ Shortcomings

- ◆ What MS design?

Quads Are the Most Popular



Source: R&D Magazine

Ion Trajectory Simulation for Orthogonal-Acceleration TOFMS

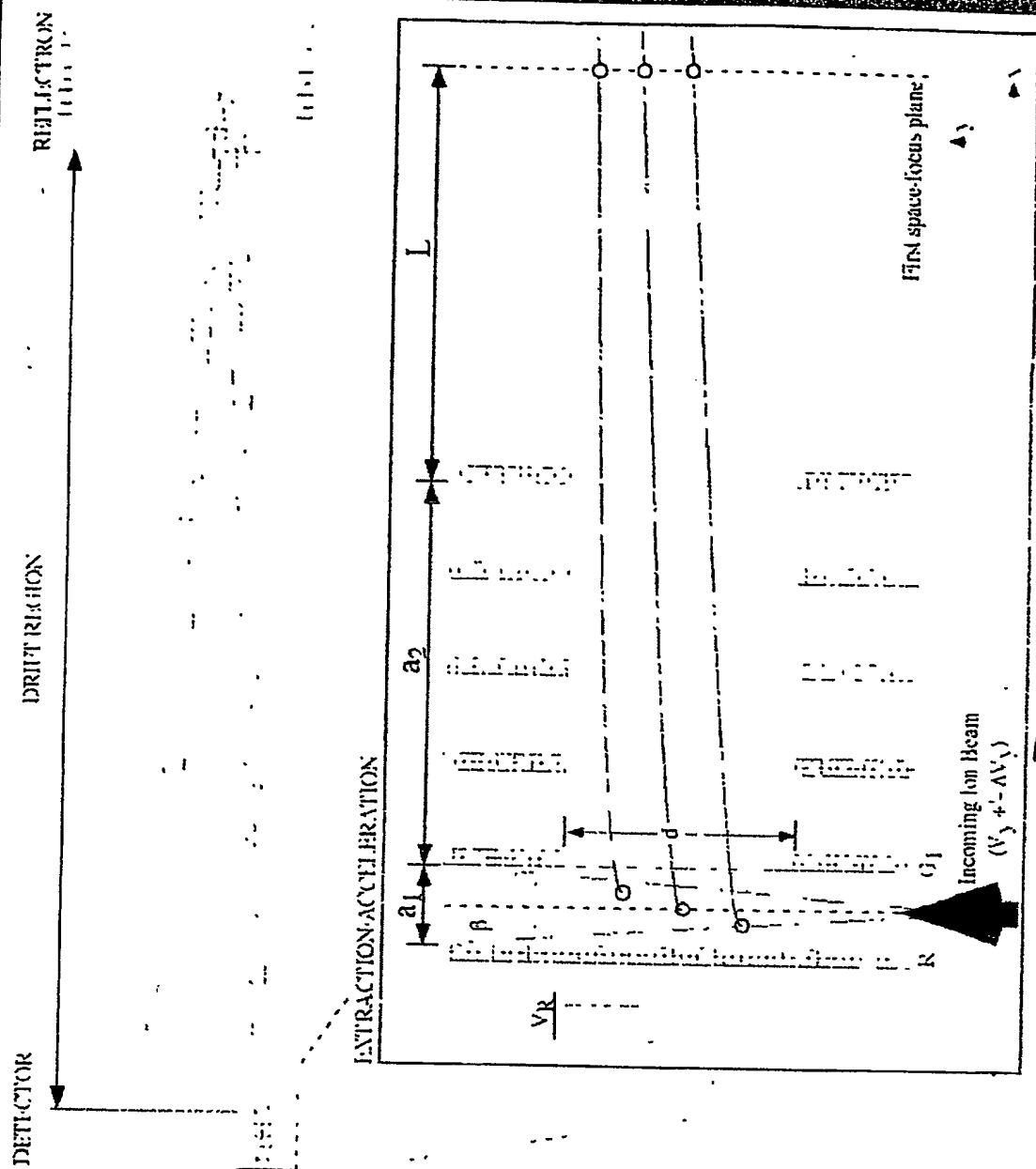


Fig-18

2-D Schematic of Dual-Source TOFMS

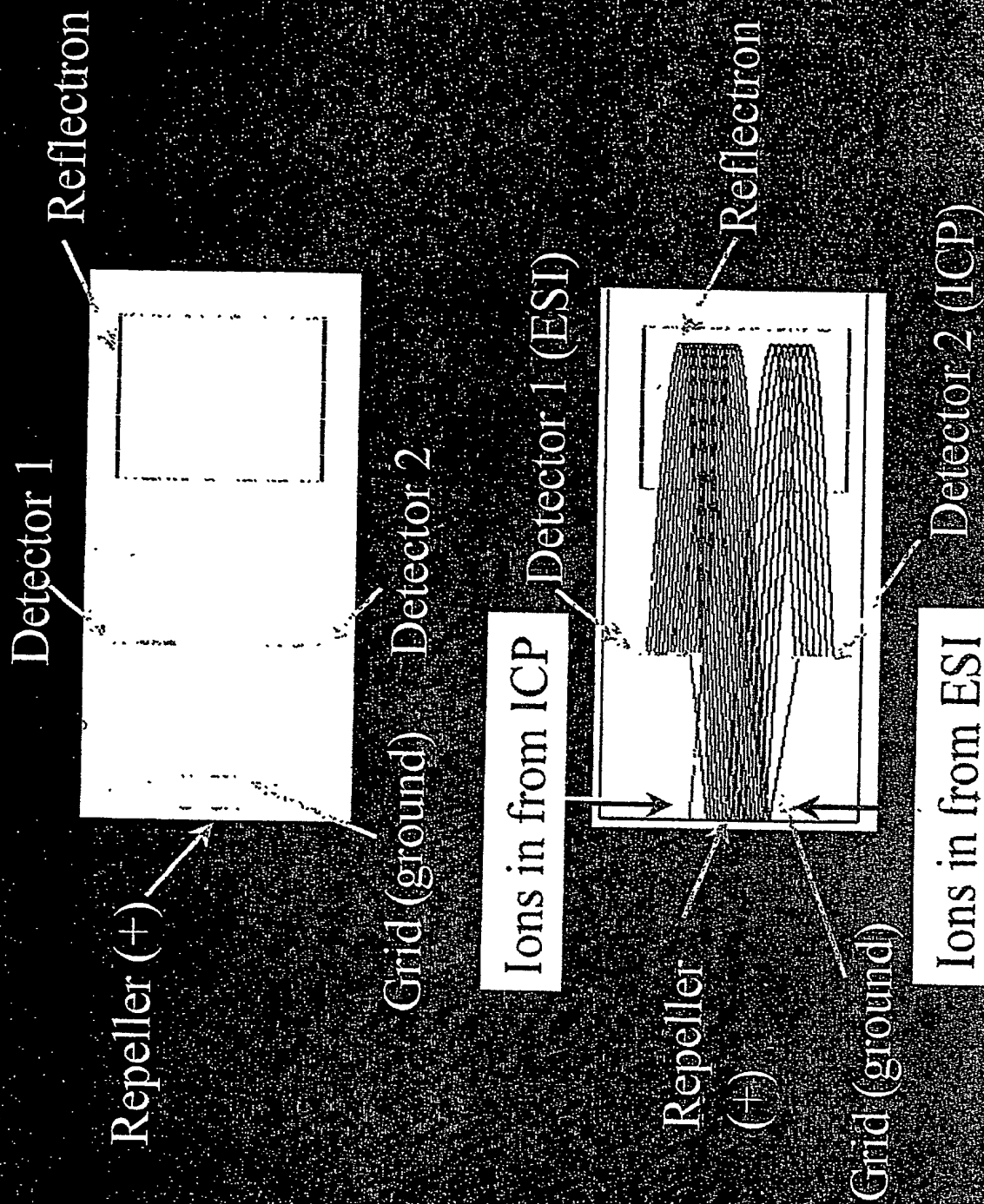


Fig. 2D

SIMION Representation of Dual-Source TOFMS

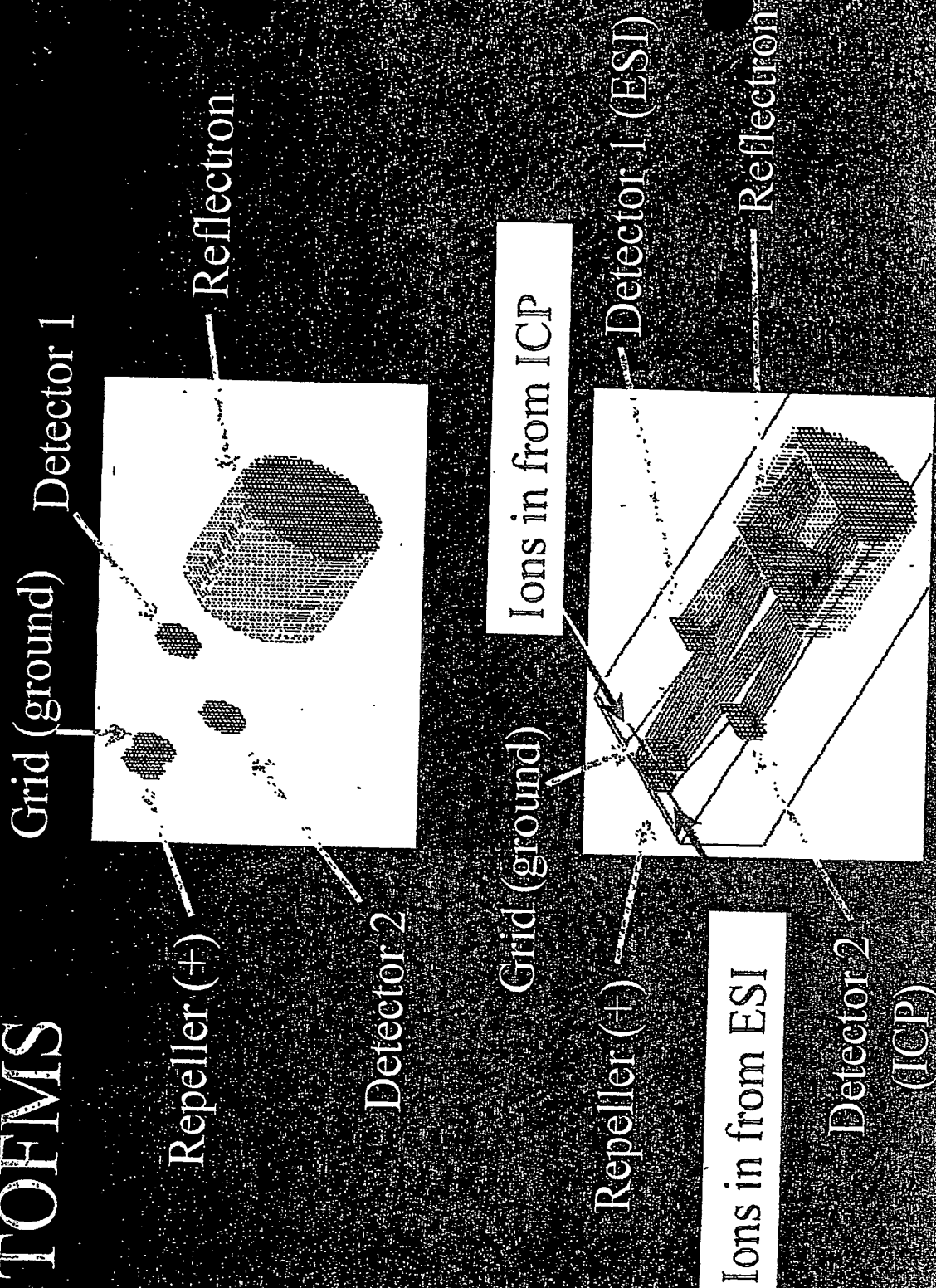
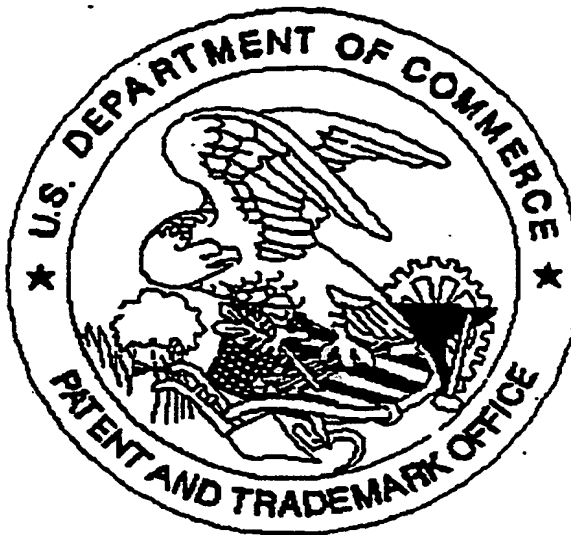


Fig 2.1

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